

Role of attractive methane-water interactions in the potential of mean force between methane molecules in water

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On the basis of a gaussian quasi-chemical model of hydration, a model of *non* van der Waals character, we explore the role of attractive methane-water interactions in the hydration of methane and in the potential of mean force between two methane molecules in water. We find that the hydration of methane is dominated by packing and a mean-field energetic contribution. Contributions beyond the mean-field term are unimportant in the hydration phenomena for a hydrophobic solute such as methane. Attractive solute-water interactions make a net *repulsive* contribution to these pair potentials of mean force. With no conditioning, the observed distributions of binding energies are *super-gaussian* and can be effectively modeled by a Gumbel (extreme value) distribution. This further supports the view that the characteristic form of the unconditioned distribution in the high- ϵ tail is due to energetic interactions with a small number of molecules. Generalized extreme value distributions also effectively model the results with minimal conditioning, but in those cases the distributions are sufficiently narrow that details of their shape aren't significant.

I. INTRODUCTION

It is generally accepted that hydrophobic effects are an essential contribution to the stability of the functional structures of soluble proteins.¹ After Frank and Evans² and then Kauzmann,³ hydrophobic effects have been identified by distinctive unfavorable entropies of hydration and large hydration heat capacities. That has made development of a fully defensible molecular theory of hydrophobic effects an outstanding challenge for statistical thermodynamics of solutions.

Over the past decade, however, such a defensible molecular theory has begun to take shape.^{4,5} Those developments^{6,7,8,9} started principally from the scaled-particle models,¹⁰ but also defined a connection to the Pratt-Chandler theory.^{11,12,13} In view of those developments, consolidation of previous work is to be expected.⁴ This paper addresses the contributions of attractive interactions, *e.g.*, dispersion interactions, on the potentials of the average forces between small hydrophobic solutes in water. That is a topic of specific interest that has been left unresolved.

Much of that specific interest is associated with the Pratt-Chandler theory which was the first serious theoretical prediction of the potential of mean force, *pmf*, between simple hydrophobic solutes in water.⁹ A paper¹⁴ which followed the initial Pratt-Chandler predictions treated the role of attractive solute-solvent interactions, and addressed an apparent disagreement with experiment that had surfaced.¹⁵ By now, a significant body of simulation data has accumulated on those *pmfs*. In the following, we briefly note those results salient to our goals. But even more, a recent theoretical insight¹⁶ seems to provide just the analysis tool needed to organize and clarify the accumulated simulation data, and to clarify the theoretical understanding of these *pmfs*.

The apparent disagreement involved the temperature dependence of the osmotic second virial coefficient

$$B_2 \equiv -\frac{1}{2} \int \left(e^{-w_{AA}(r)/kT} - 1 \right) 4\pi r^2 dr, \quad (1)$$

where $w_{AA}(r)$ is the *pmf* between two hydrophobic solutes A, assumed to be spherical in the original Pratt-Chandler theory which treated hard-sphere solutes. The *sign* of B_2 predicted for hard-sphere solutes by the Pratt-Chandler theory depended on the size of the solute, the predictions for larger solutes was attractive $B_2 < 0$. But the magnitude of B_2 decreased with increasing temperature, so the effective attractive interactions were predicted to become less attractive as the temperature was raised. The general expectation for hydrophobic interactions always had been that B_2 should be negative, indicating a net attraction, and increasing in strength with increasing temperature. Subsequent experiments for the non-spherical A = C₆H₆ (benzene)^{17,18} and for A = C₆F₆ (perfluoro-benzene)¹⁹ were consistent with the general expectation for hydrophobic interactions: this is a favorable *and endothermic* association, *i.e.*, this is an entropy driven association. Though later results have revised that endothermicity for benzene association to smaller values,²⁰ simulation results on model spherical solutes in water agree with the prior expectation for hydrophobic interactions.^{21,22}

We note also that study of the benzene-benzene *pmf* by direct numerical simulation has produced results in rough agreement with the experiments.^{23,24,25,26} These are sufficiently challenging calculations, however, that those simulation results may not be definitive for B_2 . A significant result of those calculations is that the T-shaped benzene-benzene contacts are more favorable than stacked configurations.^{24,25,26} This seems to be qualitatively different from the case studied with purely

repulsive model plates stacked.²⁷ This detail suggests a general conclusion that attractive solute-solvent interactions can play a qualitative role in establishing the most probable contacts. That realistically modelled benzene dimers and toluene dimers may differ significantly in this regard²⁶ indicates yet again that realistic details of the cases considered may decisively affect these contacts.

For spherical hydrophobic solutes, the case of Kr(aq) has received special attention. Whether $B_2 > 0$ follows from the experimental solubilities of Kr(aq) is undecided,²⁸ but relying on simulation results again, we do know that it is a realistic possibility.²⁹ Those simulation results, furthermore, do suggest that the sign of B_2 can change with the strength of solute-solvent attractive interactions. With the potential of mean force for a C60 pair,³⁰ in a different size regime, attractive interactions make a dominating contribution that is *repulsive* in character.

The work of Pangali *et al.*,³¹ indicated that the original Pratt-Chandler theory was valid for $w_{AA}(r)$ in the case where the predicted contribution of attractive interactions was small.¹⁴ Furthermore, the theory of Ref. 14 was observed by Smith & Haymet³² on the basis of molecular simulation to be strikingly accurate for $w_{AA}(r)$ pointwise in the Lennard-Jones model case there considered for which the predicted contribution of attractive interactions was large. For that case $B_2 > 0$.³² Nevertheless, the underlying Pratt-Chandler theory was the source of an inaccurate association of that Lennard-Jones model with CH₄(aq). As an example of the type of inaccuracy that should be expected, the original Pratt-Chandler theory is approximate even at small solute sizes for the case of a hard-sphere solvent.³³ Thus the accuracy of the *pmf* result for that case³² was not developed further.

The observations above suggest the following general hypotheses: (a) the balance of attractive interactions can play a significant role in hydrophobic interactions; (b) with attractive interactions included the original Pratt-Chandler theory can be accurate for the hydrophobic interactions expressed by $w_{AA}(r)$. The original Pratt-Chandler theory for hydrophobic *hydration* problems was less accurate. But the modern revisions of that theory address those hydration problems first,⁴ and largely on the basis of scaled-particle approaches¹⁰ which are by now well-developed.^{5,34} (c) $B_2 > 0$ is a realizable possibility, but probably not for the cases of general experimental interest.

In response to the apparent experimental disagreement noted above, a variety of complications were considered: (a) context hydrophobicity which, for example, might be expressed in experiments on solutes such as methanol in aqueous solution.³⁵ (b) non-spherical shapes of molecules of experimental interest;³⁶ and (c) the influence of attractive solute-solvent attractive interactions.¹⁴ These are all valid general concerns. But the *post hoc* conclusion has been that the underlying Pratt-Chandler theory is sufficiently unconvincing that extensions and elaborations have not been compelling.

Though the intuitive proposal of Ref. 14 for inclusion of attractive interactions worked-out accurately in some cases tested,^{31,32} there is a logical complication. It is common to assume that attractive interactions may be included perturbatively *after* packing problems dominated by repulsive solute-solvent interactions are solved. Then it is expected that attractive interactions may change thermodynamic properties significantly while making small alterations to structural characteristics. Being an integrated quantity, B_2 is a thermodynamic property and should be expected to be sensitive to inclusion of attractive interactions, from this perspective. But the assumed insensitivity of structural characteristics has not been so carefully examined; a physical comment about the complicated role of hard-core models of hydrophobic solutes was attempted in Ref. 5, and further observations on the role of attractive interactions in hydrophobic solubility models were made by Paschek.³⁷

A first perspective on the complications that can arise in starting from hard-core model solutes is that those complications are precursors of the drying that is expected on large length scales.¹⁰ Drying has been discussed broadly in recent times.^{38,39} Similarly, the startling success of the information theory approach for hard-sphere solutes of intermediate size^{8,40} derives from a balance of errors, approximate treatment of packing problems balanced by neglect of incipient drying.⁴ An additional perspective is that the difficulties of the original Pratt-Chandler theory are associated with detailed problems of Percus-Yevick-analogue theories as was noted above.³³ Multiple complications of different types makes correcting a reference (hard-core) theory tricky. Nevertheless, the status of the Pratt-Chandler theory for hard-sphere solutes in water has changed⁴, and the amended theory is now a compelling approximate theory — a quasi-chemical theory⁴ — relying on and acknowledging copious empirical input.^{8,40,41,42,43}

With this context, the work of Ref. 16 provides a key to theoretical assessment of the role of attractive interactions for these problems. That theory utilizes a result for the hard-core problem to address cases with attractive interactions, but the logical status of the hard-core result is *not* that of a reference system. There is no uncontrolled assumption of linear perturbative treatment of attractive interactions. Indeed, below we calculate non-linear contributions of two distinct types beyond non-hard-core interactions and an intuitively recognizable mean-field contribution, as is discussed below. Characterization and testing of this alternative theory for such a *pmf* is thus the target of this paper.

II. THEORY

We recapitulate the gaussian model of hydration and in the process also set the notation. Then we consider the extension of the theory to describe the potential of mean force between two methane molecules in water.

On the basis of the inverse form of the potential distribution theorem, the excess chemical potential of methane(aq), μ_M^{ex} , is given by

$$e^{\beta\mu_M^{\text{ex}}} = \langle e^{\beta\varepsilon} \rangle = \int P_M(\varepsilon) e^{\beta\varepsilon} d\varepsilon, \quad (2)$$

$\beta = 1/k_B T$, where T is the temperature. $\langle \dots \rangle$ specifies averaging on the basis of the probability density function $P_M(\varepsilon) = \langle \delta(\varepsilon - \Delta U_M) \rangle$, which defines the distribution of binding energies of the solute with the solvent. For a particular configuration, the binding energy $\Delta U_M = U_{N+1} - U_N - U_1$ is the difference in the potential energy of the whole system (U_{N+1}) and the sum of the (decoupled) potential energies of the solution (U_N) and the solute (U_1). Eq. (2) is independent of the simulation ensemble in the macroscopic limit and an excellent approximation for system sizes considered in this work⁴⁴.

Notice that the exponential weighting exhibited by Eq. (2) emphasizes high binding-energy contributions to $P_M(\varepsilon)$. These high energy contributions reflect collisions at short-range between the solute and the solvent particles. These high- ε (low-probability) features also render the direct application of Eq. (2) problematic.

Instead we *regularize* of the statistical problem as follows: Consider a hard-core (HC) solute that excludes water oxygen atoms from a spherical region of radius λ centered on the methane. $\mu_{\text{HC}}^{\text{ex}}$, the excess chemical potential of this hard-core solute, is assumed to be known. On the basis of simulation data obtained from a calculation on methane-water system with realistic interactions, $\mu_{\text{HC}}^{\text{ex}}$ is given by

$$e^{-\beta(\mu_{\text{HC}}^{\text{ex}} - \mu_M^{\text{ex}})} = \langle e^{-\beta(\varepsilon_{\text{HC}} - \varepsilon)} \rangle. \quad (3)$$

ε_{HC} is the binding energy of the hard-core model solute; this is zero when no water molecules overlap the hard-core model solute and is infinite otherwise. ε is the binding energy of M. The use of Eq. (3) requires eliminating configurations in which a solvent molecule penetrates the assigned hard-core exclusion volume in a simulation of M in water. The fraction of configurations thus selected is $p_M(n_\lambda=0)$. Then

$$\begin{aligned} \beta\mu_M^{\text{ex}} &= \beta\mu_{\text{HC}}^{\text{ex}} + \ln p_M(n_\lambda=0) \\ &+ \ln \int P_M(\varepsilon|n_\lambda=0) e^{\beta\varepsilon} d\varepsilon. \end{aligned} \quad (4)$$

Here $P_M(\varepsilon|n_\lambda=0)$ is the binding energy distribution conditional on the event that there are no overlaps with the defined hard-core model solute. The virtue of the regularization is that the troublesome high- ε features are accounted for by $\mu_{\text{HC}}^{\text{ex}}$ and $p_M(n_\lambda=0)$. The process is one of pushing the water molecules away from the solute. Thus by controlling the spatial distribution of molecules we temper the binding energies. The binding energies remaining after regularization are less energetic. They are composed of contributions from numerous sources, distant and thus weakly correlated. It is expected that

$P_M(\varepsilon|n_\lambda=0)$ will be well described by a normal distribution. If $P_M(\varepsilon|n_\lambda=0)$ is modelled as a Gaussian distribution, then

$$\begin{aligned} \beta\mu_M^{\text{ex}} &\approx \beta\mu_{\text{HC}}^{\text{ex}} + \ln p_M(n_\lambda=0) \\ &+ \beta \langle \varepsilon | n_\lambda=0 \rangle + \frac{\beta^2}{2} \langle \delta\varepsilon^2 | n_\lambda=0 \rangle. \end{aligned} \quad (5)$$

This approach has been tested on the case of hydrophobic $\text{CF}_4(\text{aq})$ ¹⁶ and on the case of liquid water in more than one way.^{45,46} The balance between the packing and chemical contributions to Eq. (5), $\mu_{\text{HC}}^{\text{ex}}$ and $k_B T \ln p_M(n_\lambda=0)$, respectively, and particularly with changes in the volume of the defined inner-shell has been considered explicitly. A detailed point of note is that if the inner-shell is chosen small enough, then $\ln p_M(n_\lambda=0) \approx 0$, but the packing contribution $\mu_{\text{HC}}^{\text{ex}}$ is non-zero. Then as the volume of the inner-shell is reduced, the packing contribution should be taken to be the *largest* value consistent with $\ln p_M(n_\lambda=0) \approx 0$ to sufficient accuracy. Thus, for example, with this prescription the gaussian estimate of the free energy of $\text{K}^+(\text{aq})$ ⁴⁷ can be slightly but distinctly improved by adding the appropriate packing contribution.

With the free energy Eq. (5) in hand, the entropy can be accessed through the thermodynamic identity

$$\begin{aligned} T \left(\frac{\partial S}{\partial n_M} \right)_{T,p,n_W} &= \left(\frac{\partial \langle E \rangle}{\partial n_M} \right)_{T,p,n_W} \\ &+ p \left(\frac{\partial \langle V \rangle}{\partial n_M} \right)_{T,p,n_W} - \mu_M. \end{aligned} \quad (6)$$

The ideal contributions to these thermodynamic quantities aren't specifically interesting, so we subtract the corresponding relation that obtains when the interaction potential energies vanish. Recalling that

$$\left[\left(\frac{\partial \langle V \rangle}{\partial n_M} \right)_{T,p,n_W} \right]_{\text{ideal}} = \frac{k_B T}{p}, \quad (7)$$

yields

$$\begin{aligned} T \left(\frac{\partial S^{\text{ex}}}{\partial n_M} \right)_{T,p,n_W} &= \left(\frac{\partial \langle U \rangle}{\partial n_M} \right)_{T,p,n_W} \\ &+ p \left(\frac{\partial \langle V \rangle}{\partial n_M} \right)_{T,p,n_W} - k_B T - \mu_M^{\text{ex}}. \end{aligned} \quad (8)$$

Here $\langle U \rangle$ is the expected value of the potential energy of the system. The contribution of the partial molar energy involves the mean binding energy — without the conditioning discussed above — but also the alteration of solvent-solvent interactions due to the presence of the solute. The significance of this term can be appreciated by considering the case of hard-sphere model methane. Then the theory Eq. (5) without the outer-shell interaction contributions is transparently correct, and the partial molar energy contribution to Eq. (8) involves only changes in solvent-solvent interactions.

Similarly, it is helpful to discuss the contribution to Eq. (8) associated with the partial molar volume. The magnitudes of solute partial molar volumes for hydrophobic solutes are similar to, typically somewhat smaller than, molecular van der Waals volumes. For moderate pressures and in view of the the typical low solvent compressibility, the contribution from the actual partial molar volume is negligible. The net contribution from the *excess* partial molar volume in Eq. (8) amounts invariably to $-k_B T$, the specific value of the full partial molar volume in Eq. (8) being numerically irrelevant.

III. METHANE-METHANE POTENTIAL OF MEAN FORCE

Now let us consider how to use this statistical thermodynamic model to analyze the methane-methane *pmf*. Consider a first methane molecule centered at the origin. In fact, we will use a united-atom representation of the methane molecule. Then focus on the distribution of a second methane molecule in the field of the first. That distribution can be analyzed beginning from the principle of constancy of the chemical potential in non-uniform systems⁴⁸

$$\begin{aligned} \rho_M(\mathbf{r}) &= \left(\frac{e^{\beta\mu_M}}{\Lambda_M^3} \right) e^{-\beta u_{MM}(r)} \langle e^{-\beta\Delta U_M} | \mathbf{r} \rangle_0 \\ &= \rho_M e^{-\beta u_{MM}(r)} \left(\frac{\langle e^{-\beta\Delta U_M} | \mathbf{r} \rangle_0}{\langle e^{-\beta\Delta U_M} \rangle_0} \right). \end{aligned} \quad (9)$$

Here $u_{MM}(r)$ is the assumed M-M pair interaction potential energy function, and Λ_M is the thermal deBroglie wavelength for a methane molecule. The brackets $\langle \dots \rangle_0$ indicate a *test particle* average, *i.e.* averaging in the absence of coupling between the medium and the second M molecule. ΔU_M is the binding energy of the second M molecule with the rest of the solvent medium. The conditional test-particle average $\langle \dots | \mathbf{r} \rangle_0$ is for the second M at position \mathbf{r} . The unconditional average will be practically equal to the conditional average for positions \mathbf{r} well separated from the first M molecule at the origin. The replacement

$$\langle e^{-\beta\Delta U_M} | \mathbf{r} \rangle_0 d^3r \rightarrow \langle e^{-\beta\Delta U_M} | r \rangle_0 4\pi r^2 dr \quad (10)$$

for radial characteristics of the density profile provides the desired radial distribution function $g_{MM}(r)$ according to

$$g_{MM}(r) = e^{-\beta u_{MM}(r)} \left(\frac{\langle e^{-\beta\Delta U_M} | r \rangle_0}{\langle e^{-\beta\Delta U_M} \rangle_0} \right). \quad (11)$$

The inverse form⁴⁸ corresponding to Eq. (11) is

$$g_{MM}(r) = e^{-\beta u_{MM}(r)} \left(\frac{\langle e^{\beta\Delta U_M} \rangle}{\langle e^{\beta\Delta U_M} | r \rangle} \right). \quad (12)$$

In this case, the second M molecule is physically present at the radius r in carrying-out the average and thus the subscript zero (0) is absent. The numerator in Eq. (12) is the average for a solitary M molecule, or for the second M molecule infinitely removed from the first one located at the origin. The desired *pmf* is then

$$-kT \ln g_{MM}(r) = u_{MM}(r) + \Delta w_{MM}(r), \quad (13)$$

which defines $\Delta w_{MM}(r)$, and then further denotes

$$\Delta w_{MM}(r) + \mu_M^{\text{ex}} = kT \ln \langle e^{\beta\Delta U_M} | r \rangle. \quad (14)$$

Following the steps that lead to Eq. (5), here we condition simulation data for the case of two actual M present and obtain

$$\begin{aligned} \Delta w_{MM}(r) + \mu_M^{\text{ex}} &\approx \mu_{\text{HC}}^{\text{ex}}(r) + k_B T \ln p_M(n_\lambda=0|r) \\ &+ \langle \varepsilon | r, n_\lambda=0 \rangle + \langle \delta \varepsilon^2 | r, n_\lambda=0 \rangle / 2kT. \end{aligned} \quad (15)$$

(The averaging is over a probability density distribution $P_M(\varepsilon|r) = \langle \delta(\varepsilon - \Delta U_M) | r \rangle$.) These formulae apply to the second M molecule physically present at radius r with the first M molecule located at the origin, and the indicated binding energies ε are for the second M molecule. Nevertheless,

$$\mu_{\text{HC}}^{\text{ex}}(r) \equiv -k_B T \ln p(n_\lambda=0|r) \quad (16)$$

interrogates spontaneous molecular scale cavity formation in the neighborhood of a single M molecule, the first M molecule which is located at the origin.

Eq. (15) is clearly approximate, but, as in Eq. 5, the binding energy distribution of only one M molecule is regularized. Further it is a physically motivated theory and also systematically organized. Thus, it has the advantages of physical theories, *e.g.* providing physical explanations of the observed behaviors. More specifically it is directly associated with the physical theory Eq. (5), so this approach also offers an internal calibration, in contrast to calculations of mean forces that determine the spatially varying *pmfs* but not a constant of integration.

IV. METHODS

We utilize computational results from simulations involving zero, one, and two methane molecules. A united atom representation of methane (Lennard-Jones $\varepsilon = 0.294$ kcal/mole and $\sigma = 3.73$ Å) was adopted. The SPC/E water model was used in all the simulations with the rigid H₂O structure of each water molecule controlled by the SHAKE method.

Classical molecular dynamics simulations were performed with the NAMD 2.6 code with constant NPT procedures. The pressure was held constant at 1 bar using the Langevin piston method with the Langevin piston period set at 200 fs with a decay constant of 100 fs. The temperature of 298 K was controlled by Langevin dynamics applied to the oxygen atoms. The temperature

of the Langevin piston was set equal to the temperature of the Langevin thermostat. The damping coefficient of the thermostat was set at 1 ps^{-1} .

A simulation of pure water was conducted for a system of 512 water molecules. The Lennard-Jones interaction was terminated at 10.5 \AA by smoothly switching to zero starting at 10 \AA . Electrostatic interactions were treated with the particle mesh Ewald method with a grid spacing of approximately 0.75 \AA . A well-equilibrated box of water molecule was used and a further equilibration for 250 ps was conducted. The production run lasted 750 ps and configurations were saved every 0.2 ps for analysis. $\beta\mu_{\text{HC}}^{\text{ex}}$ was evaluated by trial insertions into liquid water. Similarly, we estimated the test particle distribution $P_{\text{M}}^{(0)}(\varepsilon) = \langle \delta(\varepsilon - \Delta U) \rangle_0$ on the basis of about 2.7 million trial insertions of the methane into these water systems.

For the methane in water simulation, a methane molecule was placed in the center of the water box. For convenience in analysis, the methane was held fixed. The system was extensively equilibrated for over 2 ns. The production run lasted 4 ns and configurations were saved every 0.5 ps. FIG. 1 shows the CO radial distribution function observed.

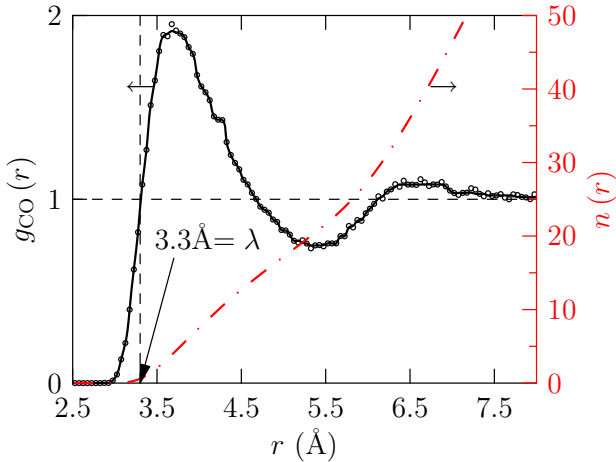


FIG. 1: The radial distribution function of water oxygen atoms around methane. 3.3 \AA , the smallest distance for which $g_{\text{CO}}(r) = 1$, is chosen as the radius λ of the inner shell.

$P_{\text{M}}(\varepsilon)$ was assessed and its overlap with $P_{\text{M}}^{(0)}(\varepsilon)$ was used to estimate $\mu_{\text{M}}^{\text{ex}}$ according to the standard relation $k_{\text{B}}T \ln P_{\text{M}}(\varepsilon)/P_{\text{M}}^{(0)}(\varepsilon) = -\varepsilon + \mu_{\text{M}}^{\text{ex}}$. A conditioning radius of 3.3 \AA was adopted in considering $P_{\text{M}}(\varepsilon|n_{\lambda}=0)$. Thus only configurations in which no water molecules come closer than 3.3 \AA to the methane are retained for analysis. The same conditioning radius is used in all the gaussian models below. FIG. 2 shows the unconditional and conditional energy distributions.

To compute $\mu_{\text{HC}}^{\text{ex}}(r)$ we adopted the following approach. For each radial distance from the methane, 572 points were placed to cover a sphere uniformly. Observation spheres of radius 3.3 \AA were placed at each point and the water occupancy statistic compiled. Statistics were

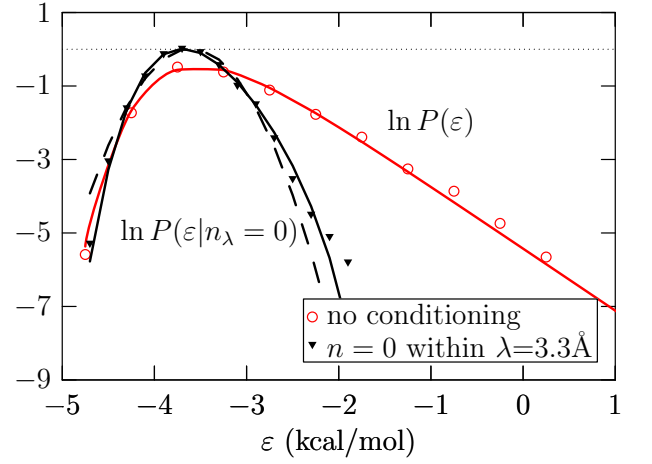


FIG. 2: Distribution of binding energies of methane to water. The open circles are the unconditional distribution $P_{\text{M}}(\varepsilon)$. The filled circles are the conditional distribution $P_{\text{M}}(\varepsilon|n_{\lambda}=0)$ obtained from the sample in which no water O-atoms occupy the volume defined by distances $\leq 3.3 \text{ \AA}$ from the methane center. The dashed curve is a gaussian model for the conditional distribution. The solid curves are generalized extreme value⁴⁹ distributions fitted to the data. For the conditioned distribution this is the Frechet extreme value distribution $\ln P(\varepsilon) = (n-1) \ln(1 - (\frac{\varepsilon-a}{nb})) - (1 - (\frac{\varepsilon-a}{nb}))^n - \ln b$ with $n = 6.34$, $a = -3.76$, and $b = 0.37$. The model plotted for the unconditioned distribution is the Gumbel extreme value distribution discussed in the text.

accumulated from 8000 frames for about 4.6 million sample points. $p(0|r)$, the probability that the observation volume is empty immediately gives $\mu_{\text{HC}}^{\text{ex}}(r)$ according to Eq. (16).

The theory above was tested against numerically exact results obtained by an overlap method as follows. Firstly, we obtained the distribution $P_{\text{M}}(\varepsilon|r)$ of binding energies of one of two methane molecules that are present in a water system, the two methane molecules being placed along the box diagonal at various separations, r , ranging from 4 \AA to 8 \AA in $\Delta r = 0.2 \text{ \AA}$ intervals. The molecules were held fixed and the system equilibrated for over 1 ns. A production run 750 ps long was conducted with configurations saved every 0.2 ps. Secondly, we obtained the distribution $P_{\text{M}}^{(0)}(\varepsilon|r)$ of a test molecule positioned at r in a corresponding simulation of water and *one* methane molecule. These distributions are related by

$$\frac{P_{\text{M}}(\varepsilon|r)}{P_{\text{M}}^{(0)}(\varepsilon|r)} = e^{-(\varepsilon - \Delta w_{\text{MM}}(r) - \mu_{\text{M}}^{\text{ex}})/kT}. \quad (17)$$

Thus, evaluation of these distributions accurately enough to determine this ratio through an intermediate ε regime determines $\Delta w_{\text{MM}}(r) + \mu_{\text{M}}^{\text{ex}}$.

V. RESULTS AND DISCUSSION

FIG. 1 shows the distribution of water oxygen atoms radially from the methane carbon. $\lambda = 3.3 \text{ \AA}$ is the smallest distance for which $g_{\text{CO}}(\lambda) = 1$. Below this radius, the influence of repulsive interaction dominates the interactions, and the conditional density of water becomes low. We define the radius of the hard sphere to be this value, and the probability $p_M(n_\lambda = 0)$ follows from that. Here that probability is about $p_M(n_\lambda = 0) \approx 0.6$, so the conditioning eliminates only about half of the total number of configurations. The *mean* number of water O-atoms with $r < \lambda$ is also about 0.6. From this we can conclude that $n_\lambda = 1$, and $n_\lambda = 2$ are about equally likely with probability of 0.2.

This minimal conditioning, nevertheless, has a dramatic affect on the distribution of binding energies as FIG. 2 shows. The extended tail seen there in the unconditional distribution reflects the high-energy short-range collisions between the methane solute and the nearest few water molecules, as discussed above. The conditioning excludes those high- ε interactions and the remaining interactions conform to the anticipated gaussian distribution. For the conditional distribution $\langle \varepsilon | n_\lambda = 0 \rangle = -3.6 \text{ kcal/mole}$, whereas $\langle \varepsilon \rangle = -3.2 \text{ kcal/mole}$. Based on the fraction of configurations that contribute to the conditional distribution, evacuation of the inner-shell requires the modest energy $-k_B T \ln p_M(n_\lambda = 0) = 0.29 \text{ kcal/mole}$. The latter quantity is the chemical contribution identified in earlier quasi-chemical generalizations of the potential distribution theorem.^{16,45} The fluctuation contribution $\langle \delta \varepsilon^2 | n_\lambda = 0 \rangle / 2kT = 0.13 \text{ kcal/mole}$. This is about 4% of the mean binding energy. Thus a mean-field approximation is adequate to describe the hydration of methane. By trial insertions, we estimate $\mu_{\text{HC}}^{\text{ex}} = 6.08 \text{ kcal/mole}$, in good agreement with the value of 6.2 kcal/mole predicted by revised scaled particle theory⁵. Thus on the basis of Eq. (5), $\mu_M^{\text{ex}} = 2.32 \text{ kcal/mole}$, in excellent agreement with the value of 2.38 kcal/mole obtained on the basis of the overlap method (see also Ref. 44).

We used Eq. (8) to obtain a direct evaluation of the entropy of the M solute. The remaining difficulty, which is serious, is the potential for catastrophic loss of precision in performing a subtraction to evaluate the partial molar excess internal energy, $(\partial \langle U \rangle / \partial n_M)_{T,p,n_W}$. We followed^{50,51} in considering the mean binding energies of water molecules within a sphere surrounding the solute, and seeking saturation and plateau behavior with increasing radius of the sphere. We note again that the present calculation permitted the volume of the simulation cell to fluctuate with p (the pressure) specified, and we also note that the system size for the present calculation is only 512 molecules. We found, however, the mean net solvent binding energies to the solvent for water molecules in the second hydration shell of the solute was roughly zero to within statistical uncertainties of more than ten kcal/mol. In the first hydration shell that

mean net solvent binding energy of water to the solvent was about one kcal/mol, *positive*, within large statistical uncertainties but decidedly less than ten kcal/mol. The mean unconditioned solute-solvent binding energy was -3.2 kcal/mol. The roughly estimated partial molar energy is thus about -2.0 kcal/mol. This number is in good agreement with experiment,⁵² and thus the value for the entropy is satisfactory as well. The first such *direct* entropy evaluation, for liquid water,⁴⁵ was strikingly simple, but here the study of the temperature dependence of the free energy would be more efficient. An important physical point is that this evaluation reinforces the conclusion that solvent-solvent interactions in the neighborhood of a primitive hydrophobic solute can be *positive*, a point emphasized recently by conclusive results for hard-sphere solutes.⁵ This point suggests limitations in the classic iceberg or clathrate pictures of hydrophobic hydration. Of course, such values are expected to be strongly temperature dependent.

FIG. 2 also shows that extreme value distributions⁴⁹ are effective in modeling the distributions $P(\varepsilon)$, particularly the unconditioned distribution. The high- ε behavior is faithfully exponential, and the Gumbel extreme value distribution $\ln P(\varepsilon) = -(\varepsilon + 3.52)/0.59 + 0.52 - e^{-(\varepsilon+3.52)/0.59}$ is accurate. This further supports the view that the characteristic form of the unconditioned distribution in the high- ε region is due to energetic (i.e. ‘extreme’) interactions with a small number of molecules.

A gamma distribution of interaction energies has been proposed in a different statistical thermodynamic setting for closing and integrating a differential equation for an entropic equation of state.^{53,54} A gamma distribution is qualitatively satisfactory here but not as accurate as the Gumbel distribution. As does the present work, those previous studies emphasized *realizability* in free energy models: free energy evaluations can benefit from restriction to legitimate probability distributions.

A distinction from that preceding work^{53,54} is that we study here the distribution of an intensive characteristic, a possibility noted before.⁵³ Then the central limit theorem is not available to force the unconditioned distribution toward a normal (gaussian) form. Alternatively, the present theory naturally presents a physical control feature, the volume of the defined inner shell, to drive the observed conditioned distribution toward a normal (gaussian) form. With minimal conditioning as here, the conditioned distribution can be slightly *super-gaussian*. With aggressive conditioning, these binding energy distributions can become *sub-gaussian*.⁴⁵ Then an alternative model, perhaps a beta distribution, might be more effective.

Returning to the results, an important point here is that the chemical and fluctuation contributions depend weakly on r , as FIG. 3 shows.

FIG. 4 shows $\Delta w_{\text{MM}}(r) + \mu_M^{\text{ex}}$ (see Eqs. (14) and (15)). The agreement between the gaussian quasi-chemical theory and the numerically exact overlap result is close *except* in the region of the dehydration barrier. We ascribe

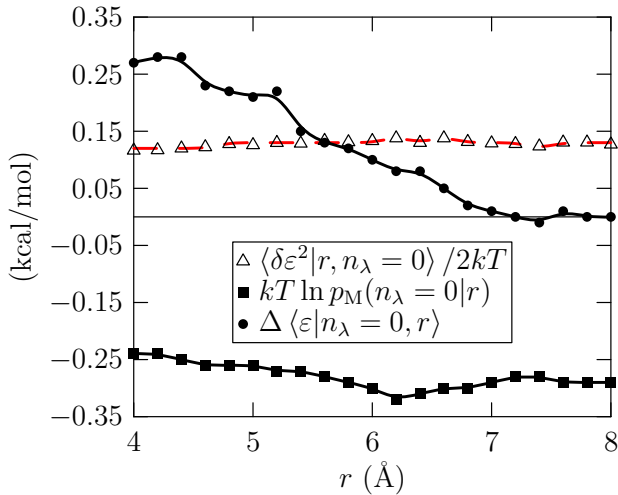


FIG. 3: Notice the slight variation with radius r of the chemical contribution $kT \ln p_M(n_\lambda=0|r)$ and the fluctuation contribution $\langle \delta \varepsilon^2 | r, n_\lambda=0 \rangle / 2kT$. The probability that one methane molecule of a pair has an empty inner-shell ($p_M(n_\lambda=0|r)$) is greatest just outside MM contact (see FIG. 4), and least just outside the predicted dehydration barrier where intervening water molecules can take effective advantage of attractive interactions with each methane molecule of the pair of methane molecules.

the discrepancy of the theory-overlap data comparison in that region to the difficulties of the present direct estimate of $p(n_\lambda=0|r)$ (see Eq. (16)), particularly in view of the evident noise in the theoretical result. Together with the results of FIGS. 2 and 3, this is strong confirmation of the physical correctness of the mean-field description of the effects of attractive interactions in these *pmfs*. FIGS. 3 and 4 together show that for molecular size solutes, and where the strength of attractive interactions with water are similar to those expressed by aliphatic groups, the packing contributions are the biggest single contribution though mean-field contribution from attractive interactions are not negligible. The net effect here of attractive solute-water interactions is *repulsive*, as was guessed before,¹⁴ and we expect that to be the usual case.

Discussion of these points, sharpens our understanding of some earlier calculations^{8,55} that utilized solely packing contributions for such pair potentials of mean force. In a precisely defined setting, such models should be augmented to include the effects of attractive forces. Just as important, information theory models for composite species that can dissociate have some peculiarities.^{4,41} It is likely that those peculiarities combined with secondary

but non-negligible affects of solute-water attractive interactions are part of the understanding of the striking initial observations of agreement of the information theory models with simulation results.⁸

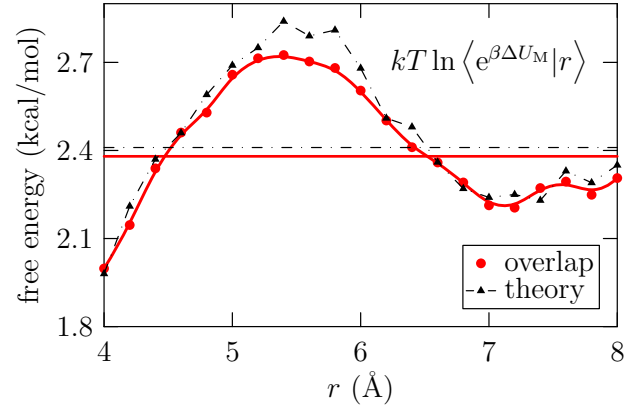


FIG. 4: The absolute solvent contribution to the potential of mean force between two methane molecules, see Eq. (14). The bold line is the reference value obtained from the overlap method of Eq. (17). The triangles are the net profile obtained using the gaussian-model, Eq. (15).

VI. CONCLUSIONS

The gaussian quasi-chemical theory is physically valid for these pair potentials of mean force. The theory here is sufficiently accurate that the packing contribution may be inferred from simulation data on the system with physical interactions. In the present approach, the packing contribution does not have the logical status of a reference system contribution in a perturbative formulation. In particular, the chemical contribution thereby defined is non-perturbative. Nevertheless, packing effects make the largest contribution, and both chemical and fluctuation contributions are negligible by comparison. For the methane-methane pair potential of mean force in water at customary conditions, mean-field effects associated with solute-water attractive interactions are secondary but not negligible. Attractive solute-water interactions make a net *repulsive* contribution to these pair potentials of mean force. This substantiates a previous physical guess,¹⁴ and is consistent with intervening observations.³² Extreme value distributions accurately model the distributions observed here, which are *super-gaussian*.

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